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RESEARCH HIGHLIGHT

Killing the Buζζ: accumbal PKMζ blunts cocaine seeking and reward

Rajani Maiya[1] and Robert O. Messing[1,2]

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Environmental cues associated with drug use are potent mediators of relapse in drug addiction [1]. Little is known about molecular mechanisms underlying these associations. In a recent issue of *Neuropsychopharmacology*, McGrath et al. [2] proposed a role for the enzyme protein kinase M zeta (PKMζ) in the nucleus accumbens (NAc) in cocaine self-administration and reinstatement.

PKMζ has been implicated in molecular mechanisms that maintain memory and long-term potentiation (LTP). PKMζ is a member of the atypical protein kinase C (PKC) subfamily and is transcribed from an internal start site within the *Prkcz* gene, which also encodes protein kinase C zeta (PKCζ). PKMζ possesses two key properties of a memory maintenance molecule: It is produced during LTP by de novo protein synthesis and is autonomously active without the requirement of second messenger stimulation. However, its role in memory maintenance is controversial. To inhibit PKMζ, early studies used the PKC inhibitor chelerythrine, a psuedosubstrate PKCζ inhibitory peptide (ZIP) or a dominant negative mutant of PKMζ to reverse LTP maintenance and disrupt long-term memory. These findings were later challenged by studies showing intact LTP and long-term memory in PKMζ knockout mice [3, 4]. Moreover, ZIP was effective in disrupting memory and LTP in PKMζ knockout mice, and current evidence indicates that ZIP and chelerythrine are not selective PKMζ inhibitors. Although a recent study using antisense oligonucleotides suggested that LTP and memory in PKMζ knockout mice are mediated by compensatory upregulation of another atypical PKC, PKCι/λ [5], such a mechanism does not explain intact LTP in adult mice with conditional deletion of hippocampal PKMζ [4].

PKMζ has also been studied in models of addiction. ZIP-mediated inhibition of PKMζ in the NAc abolished morphine CPP [6] and cocaine-induced facilitation of spontaneous excitatory transmission in the ventral tegmental area [7]. However, since these studies used ZIP, the role of PKMζ in these findings remains in question. In contrast, in their recent study, McGrath and colleagues used genetic tools to demonstrate a role for PKMζ in cocaine reward and cue-induced reinstatement of cocaine seeking.

First, the authors showed that cocaine self-administration followed by abstinence increases PKMζ mRNA and protein in the NAc, consistent with de novo synthesis of the enzyme. For this experiment, mice were first trained to self-administer food for 10 days and then cocaine for 10 days before being sacrificed 14 days later. Because of this design, it is difficult to know whether exposure to food or cocaine, or withdrawal from both increased PKMζ levels in the NAc. Nevertheless, these data are consistent with our findings that PKMζ mRNA and protein levels in the NAc are increased after exposure to a single dose of alcohol [8]. Together, these results indicate that PKMζ levels in the NAc are remarkably sensitive to drug experience.

The authors next examined cocaine self-administration and cue-induced reinstatement of cocaine seeking. Both male and female PKMζ knockout mice exhibited higher rates of responding for cocaine and increased cue-induced drug seeking than wild type controls. These results are reminiscent of the increased alcohol intake we found in PKMζ knockouts [8], and suggest a general role for PKMζ in blunting drug reward. Using floxed PKMζ mice and virally delivered Cre recombinase, the authors were able to reduce PKMζ expression by about 60% in the adult NAc and recapitulate increased cocaine taking and seeking observed in knockout mice. Importantly, Cre-mediated knockdown of PKMζ did not alter PKCι/λ, making it unlikely that compensation by PKCι/λ was a factor. Surprisingly, this effect was only observed in male mice, implicating a different brain region in females. It is not known whether PKMζ contributes to learning, memory, and synaptic plasticity in females and this should be a focus of future investigation.

To determine if these findings were cocaine-specific, the authors also examined food self-administration and cue-induced relapse to food seeking in constitutive PKMζ knockout mice. While both male and female PKMζ knockouts self-administered more food pellets than wild type mice, cue-induced food seeking was not affected in either sex. NAc-specific knockdown of PKMζ produced a similar result, suggesting a role for PKMζ in the NAc in specifically regulating cocaine self-administration and reinstatement.

If PKMζ generally facilitates long-term memory, its blunting effect on cocaine reinstatement presents an interesting paradox because the current study suggests that PKMζ interferes with the formation or expression of a cocaine memory. The answer to this paradox may lie in the dependence of different types of memory on subtypes of AMPA receptor in different brain regions. In the hippocampus, PKMζ is postulated to sustain spatial memory by increasing AMPA transmission through phosphorylation of the N-ethylmaleimide sensitive factor, which promotes trafficking of GluA2-containing AMPARs to synapses [9], and by blocking endocytosis of GluA2-containing AMPARs [10]. In contrast, a critical mechanism for cue-induced cocaine seeking involves removal of GluA2-containing AMPARs in the NAc and insertion of Ca^{2+}-permeable, GluA2-lacking AMPARs [1]. Hence in wild type

[1]Department of Neuroscience, The University of Texas at Austin, Austin, TX 78712, USA and [2]Department of Neurology, Dell Medical School, The University of Texas at Austin, 1701 Trinity St., Stop Z0700 HDB 5.320, Austin, TX 78712, USA
Correspondence: Robert O. Messing (romessing@austin.utexas.edu)

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mice, cocaine-induced increases in PKMζ may prevent removal of synaptic, GluA2-containing AMPARs, thereby blunting cocaine seeking. Interestingly, several studies have shown that manipulating AMPAR function in the NAc does not affect food seeking, which further supports the idea that PKMζ may be functioning through AMPARs in the NAc. Future studies will need to examine this hypothesis directly by examining cell surface GluA2-containing AMPARs in the NAc after PKMζ knockdown and whether manipulations hypothesized to block removal of GluA2-containing receptors, such as overexpression of PKMζ, will prevent increased cocaine seeking and taking in PKMζ knockouts.

In summary, McGrath et al. have shown that PKMζ in the NAc serves a protective function by blunting cocaine reward and reinstatement. These results indicate a more dynamic role for PKMζ in memory than previously appreciated. More work is needed to elucidate mechanisms by which PKMζ regulates cue-reward associations. Understanding these mechanisms could eventually yield novel pharmacotherapies for addiction.

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ADDITIONAL INFORMATION

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